AM

L-19-0033

Chemical Name: [redacted]
CASRN: none

ASSIGNMENTS	NAME	DATE
SAT Chair	Dortiza Pagan-Rodriguez	12/4/18
HH Hazard Assessor (A)	Keith Salazar	12/4/18
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Human Health Report Status:		DATE COMPLETED
X	HAZARD DRAFT- Pending Review	12/7/18
X	HAZARD REVIEWED	12/19/18
X	HAZARD FINAL	12/20/18
X	RISK DRAFT- pending review	12/20/18
X	RISK REVIEWED	12/20/18
	RISK-FOCUS FINAL- Uploaded	
	POST-FOCUS UPDATE DRAFT	
X	POST-FOCUS UPDATE FINAL- Uploaded	06/07/19

Updated on 6/6/19: Included new information provided by the submitter to revise the assessment.

1 HUMAN HEALTH SUMMARY

EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties and by comparing it to structurally analogous chemical substances for which there is information on human health hazard.

Based on the hazard determination and additional structure-activity analysis, EPA did not identify risks for the PMN substance.

1.1 Hazard Summary

1.1.1 Absorption / Metabolism

Absorption of the neat substance estimated to be nil all routes (pchem). The new chemical substance is expected to undergo urethane bond hydrolysis in the stomach, releasing a perfluoro compound ([redacted]), which has test data showing systemic hazards.

1.1.2 Structural Alerts

Waterproofing, [redacted]

1.1.3 Hazard Concerns

- Lung effects based on analogy to chemicals with waterproofing properties.
- Systemic (kidney) toxicity based on acidic degradation to [redacted] in the stomach or in the environment.

1.1.4 Hazard Summary (narrative)

EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties and/or by comparing it to structurally analogous chemical substances for which there is information on human health hazard, and/or other structural information. Absorption of the new chemical substance is expected to be nil via all routes based on physical/chemical properties. For the new chemical substance, EPA identified lung effect hazards due to waterproofing properties based on structural alerts and systemic and reproductive toxicity hazards if the new chemical substance undergoes acidic degradation to a [redacted]. EPA quantitatively assessed the new chemical substance using test data on analogues. EPA identified a LOAEC of 1.5 mg/m^3 based on lung effects in an acute inhalation study that was used for assessing inhalation exposures (with a benchmark MOE of 300) and a $BMDL_{10}$ of 90.4 mg/kg-bw/day based on systemic effects in a 2-yr combined chronic toxicity/carcinogenicity study that was used to assess dermal and drinking water exposures (with a benchmark MOE of 23,000).

1.2 Exposure and Risk Characterization

For this assessment, exposure to workers was assessed via dermal and inhalation routes. Releases to water, air and landfill are expected. Exposure to the general population was assessed via

drinking water, fish ingestion and inhalation of fugitive air. Exposure to consumers via dermal and inhalation exposures was assessed.

1.2.1 Workers

Risks to workers for lung waterproofing were not assessed quantitatively because a structure – activity comparison between the analogue and the LVE substance indicate the LVE substance is unlikely to convey the same waterproofing characteristics as the analogue.

Dermal risks to workers were not evaluated since there is not expected to be exposure to or absorption of the parent compound by the skin.

1.2.2 General Population

Risks to the general population for lung waterproofing were not assessed quantitatively because a structure–activity comparison between the analogue and the LVE substance indicate the LVE substance is unlikely to convey the same waterproofing characteristics as the analogue. Furthermore, this acute, portal of entry effect is considered unlikely due to dilution of the new chemical substance in air immediately upon release, such that risks from inhalation exposure are expected to be negligible.

Risks were not identified for the general population for systemic effects *via* drinking water, fish ingestion, or stack air exposures to the degradation product [redacted] of the new chemical substance (MOEs $\geq$ 383,015; benchmark MOE = 23,000).

1.2.3 Consumers

Risks to consumers for lung waterproofing were not assessed quantitatively because a structure –activity comparison between the analogue and the LVE substance indicate the LVE substance is unlikely to convey the same waterproofing characteristics as the analogue.

Dermal risks were not evaluated since there is not expected to be exposure to the parent compound during use or absorption of the parent compound by the skin.

1.3 Uncertainties and Assumptions

Absorption of the LVE is based on pchem.
Metabolism is assumed to be important and is expected to degrade to [redacted] during digestion.
There are no measured data on the LVE substance itself.
Health effects are based on analogue data.
The evaluation of the LVE is based on presumed metabolite/degradant.

2 HUMAN HEALTH HAZARD- PART A

2.1 Chemistry Summary

PMN: L-19-0033	Submitter: [redacted]			Manu.	Import
Max. PV (KG): [redacted]		Binding Option Marked:		Y	X
MW: [redacted]		% < 500		% <1000	CASNO.: None

PMN Structure	Prop.	Meas.	Est.
[redacted]	MP	71 - 73	
	BP		Dec. >200
	Pres.		at 760 mm Hg
	VP		<0.000001
	S-H2O		<0.000001
	log P		14.29

Chemical Name	Analogues:
[redacted]	[redacted]
[redacted]	
Patents (same use): None.	

2.1 SAT Summary

2.1.1 Absorption

Absorption of the neat substance estimated to be nil all routes (pchem). The LVE of the substance is expected to undergo urethane bond hydrolysis in the stomach, releasing a perfluoro compound ([redacted]), which has test data showing systemic and developmental hazards.

2.1.2 SAT Health Summary

The presence of poly/perfluoro moieties suggests that the LVE substance may induce lung waterproofing.

The perfluoro degradation product has analogy to [redacted] (see same as case [redacted]).

2.1.3 Exposure Routes of Interest

Route of Interest	
x	Inhalation: -
x	Dermal:
x	Ingestion:

2.2 Toxicity Data

2.2.1 LVE Data (study summary, POD, same-as)

[redacted] **(Same as) Health summary**:

Health:

Health Summary: Absorption is nil all routes (pchem). Concerns limited to the perfluoro degradation product based on analogy to [redacted]

2.2.2 Analogue/Metabolite Data (chemical, structure, study summary, POD)

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(38) ANALOGUES:			
PMN or CAS No.	Chem. Name	Structure	TSCA Y/N
[redacted]			N
			N
			N

2.2.2.1 [redacted]

[redacted]

Health:

Health Summary: Expect moderate absorption via all routes (pchem). Concern for liver toxicity and bone effects, specifically teeth, based on submitted test data.

For the potential degradation product, based on test data for the analogue [redacted] concerns are liver toxicity, blood toxicity, and male reproductive toxicity [rat 28-day oral NOAEL = 50 mg/kg, LOAEL = 150 mg/kg with liver toxicity; rat 90-day oral LOAEL = 10 mg/kg based on decreased body weight in males at all doses and liver toxicity and anemia at 200 mg/kg; there were toxic effects on the testes in 2 males in the 90-day oral study that were judged by the reviewer to be indicative of the potential for male reproductive toxicity. There is also concern for immunosuppression and oncogenicity based on data for PFOA and PFOS.

Test Data: (-) Salmonella with and without activation; (-) E. coli with and without activation; (-) for chromosome aberrations in CHL cells with and without activation; rat inhalation LC0 = 10,000 ppm; rat dermal LD50 > 2000 mg/kg, one male died; rat oral LD0 = 2500 mg/kg; no skin irritation in rabbits; no eye irritation in rabbits; (-) for skin sensitization in a mouse local lymph node assay at 100% ai; rat 28-d oral NOEL = 40 mg/kg, LOEL = 200 mg/kg with liver toxicity and mottled teeth in males only

[redacted]

2.2.3 SDS Data (composition, hazard identification, toxicological information)

SECTION 2: Hazards identification

2.1. Classification of the substance or mixture

Classification according to Regulation (EC) No. 1272/2008	The substance or mixture is not classified.

In accordance with Regulation (EC) No. 1272/2008 (GHS/CLP), the product does not need to be classified nor labelled.

Additional information	For the full text of the phrases mentioned in this Section, see Section 16.

2.2. Label elements

Signal Word	-
Hazard Statements	None.
Precautionary statements	None.
Supplemental information	None.
Product identifier	None.
2.3. Other hazards	None known.

SECTION 3: Composition/information on ingredients

3.2. Mixtures

[redacted]

For the full text of the phrases mentioned in this Section, see Section 16.

Hazardous impurities	None known.

2.2.4 Other Information

Neat material will degrade to [redacted] in the stomach and will undergo oxidative metabolism by gut microflora to [redacted]

2.3 Human Health Category (From US EPA 2010 document)

Chemical Category: Not applicable

2.4 Point of Departure Selected and Basis

2.4.1 POD for Lung Waterproofing (Only appropriate for inhalation exposure to parent via particulate or vapor exposure)

POD type (NOAEL/LOAEL): LOAEC

[redacted]

POD Chemical: [redacted] (newer formulation identified as [redacted] and referred to hereinafter as "[redacted]"); [redacted][1] tentatively identified the formulation constituents based on comparison with mass spectral data, which provided suggestive evidence that [redacted] consisted of fluoralkene, fluorophenyl, and/or fluoroalcohol compounds. In contrast, the older formulation, which was not implicated in cases of acute lung injury, consisted of fluoroalkanes.[2]

POD Route: Inhalation (whole body)

POD Study Type: Rat, Sprague-Dawley, male; varying durations; 8 hour recovery period; 0.5 hr (1.5 mg/m^3), 1.5 hr (1.9 mg/m^3), or 2 hr (3.2 mg/m^3); Guinea Pig, English shorthair, male; 2 hour duration; 18 hour recovery period; 0 , 1.5 or 3.2 mg/m^3 doses

POD Endpoint: Lung effects based on edema, death, rapid breathing, necrosis, hemhorrage

POD Value: The lowest reported point of departure was a LOAEC of 1.5 mg/m^3

POD Basis: This POD was selected based on the waterproofing properties of the new chemical substance. Chemicals with waterproofing effects have a diverse chemical structure and the very limited data on the pulmonary effects of waterproofing chemicals. This POD is assumed to be protective for all pulmonary effects associated with waterproofing. This POD is only appropriate for quantifying risk for the parent compound.

POD Benchmark MOE: 300; the benchmark MOE consisted of the following: intra-species extrapolation (*i.e.*, human-to-human variability/uncertainty or UF_H), interspecies extrapolation (*i.e.*, animal-to-human variability/uncertainty or UF_A), and LOAEC-to-NOAEC extrapolation (*i.e.*, UF_L). The UF_H consists of a toxicokinetic (TK) and toxicodynamic (TD) component, each of which is assigned a default value of 3.16. The TK component remained at 3.16 because although the types of local effects reported (direct chemical reactivity) do not involve metabolism, no human data are available on potential kinetic factors such as excretion (i.e., breathing rates). A default TD component of 3.16 was used because of the lack of information on the sensitivity between humans for water proofing in the respiratory tract. The UF_A also consists of a TK and TD component, each of which are assigned the same default values of 3.16. The TK component was reduced to 1.0 because the types of local effects reported (direct chemical reactivity) do not involve metabolism,[3] . The default TD component of 3.16 was retained; however, for the UF_A, this value accounts for the assumed greater sensitivity of humans than animals to respiratory effects, regardless of the mode of action. A default UF_L of 10 applied because the POD for the water proofing analogue was based on a LOAEC. The overall benchmark MOE = 300.

Reference: [redacted] see Footnote 1.

[1] [redacted]

[2] *Id*.

[3] U.S. EPA Office of Research and Development (1994). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.

[redacted]

2.4.2 POD for [redacted] ([redacted] (Only appropriate for degradant released in drinking water or stack air)

POD type: NOAEL; $BMDL_{10}$, as calculated by [redacted])[4]
POD Chemical: [redacted] CASRN [redacted]
POD Route: Oral (gavage)
POD Study type: Combined chronic toxicity/carcinogenicity study in male and female rats, comparable to OECD TG 453[5]
POD Endpoint: Kidney effects (papillary necrosis and tubular degeneration)
POD Value: NOAEL=30 mg/kg-bw/day; BMDL10=90.4 mg/kg-bw/day
POD Basis: This POD is protective for all health concerns associated with [redacted] This POD is only appropriate for quantifying risk for the degradants which would occur from drinking water, landfill release, and stack incineration.
POD Benchmark MOE: 23,000 (based on differential half-life in humans compared to rats from a study on [redacted] technicians)
References: [redacted]); see Footnotes 4 and 5.

[4] [redacted]
[5] [redacted]

[redacted]

3 HUMAN HEALTH RISK (PART B)

3.1 USES and EXPOSURES

3.1.1 Uses

Intended use: [redacted]

3.1.2 Worker Exposure

3.1.2.1 Inhalation

Proc:
Inhalation exposures not expected, containers remain unopened.

Use 1:

- Vapor during heating:
  PDR = [redacted] mg/day over [redacted] days

- Particulate:
  Inhalable: [redacted] mg/day over [redacted] days/yr
  Respirable: [redacted] mg/day over [redacted] days/yr

Use 2:

- Vapor during heating:
  PDR = [redacted] mg/day over [redacted] days

- Particulate:
  Inhalable: [redacted] mg/day over [redacted] days/yr
  Respirable: [redacted] mg/day over [redacted] days/yr

Use 3:

- Mist:
  PDR: [redacted] mg/day over [redacted] days/yr

3.1.2.2 Dermal

Proc:
Dermal exposures not expected, containers remain unopened

Use 1/2: Dermal contact with solid [redacted] is non-quantifiable (some surface contact may occur if manually transferred) as LVE is entrained in solid [redacted] The dermal absorption of the PMN is expected to be NIL based on the solid physical state at room temperature, the high molecular weight and the very high log Kow value. Due to high temperature of [redacted] during application, dermal exposure to liquid [redacted] is not expected.

[redacted]

Use 3: [redacted] mg/day over [redacted] days/yr

3.1.3 General Population Exposure:

Exposure Scenario[1]	Water						Landfill	Stack Air		Fugitive Air	
Release activity(ies)[2]; exposure calculation(s)[3]	Drinking Water		Fish Ingestion		7Q10[4] CC =23	PDM Days Exceeded	LADD	ADR (24-hr conc.)	LADD (Annual conc.)	ADR (24-hr conc.)	LADD (Annual conc.)
	ADR	LADD	ADR	LADD							
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	µg/l	# Days	mg/kg/day	mg/kg/day ($\mu g/m^3$)	mg/kg/day ($\mu g/m^3$)	mg/kg/day ($\mu g/m^3$)	mg/kg/day ($\mu g/m^3$)
USE1:Max ADR	**2.15e-7**	--	**3.21e-7**	--	**1.04e-2**	--	--	-- (--)	-- (--)	**3.15e-6** (**1.72e-2**)	-- (--)
USE1:PDM	--	--	--	--	**1.04e-2**	[redacted]	--	-- (--)	-- (--)	-- (--)	-- (--)
USE1:Max LADD	--	**6.56e-10**	--	**4.40e-10**	--	--	**2.05e-6**	-- (--)	-- (--)	-- (--)	**1.29e-8** (**1.66e-4**)
USE2:Max ADR	**3.12e-6**	--	**4.67e-6**	--	**1.50e-1**	--	--	-- (--)	-- (--)	**4.01e-5** (**2.20e-1**)	-- (--)
USE2:Max LADD	--	**6.51e-10**	--	**4.37e-10**	--	--	**1.91e-6**	-- (--)	-- (--)	-- (--)	**1.11e-8** (**1.44e-4**)
USE3:Max ADR	**5.66e-5**	--	**8.47e-5**	--	**2.74e+0**	--	--	-- (--)	-- (--)	**7.25e-4 (3.96e+0)**	-- (--)
USE3:Max LADD	--	**1.97e-8**	--	**1.32e-8**	--	--	**6.23e-8**	-- (--)	-- (--)	-- (--)	**3.36e-7** (**4.34e-3**)

3.1.3.1 Drinking Water

5.66E-5 mg/kg/day

3.1.3.2 Fish

8.47E-5 mg/kg/day

3.1.3.3 Landfill

2.05E-6 mg/kg/day (LADD)

3.1.3.4 Air/Inhalation

Fugitive – 7.25E-4 mg/kg/day (3.96E+0 $\mu g/m^3$)

3.1.4 Consumer Exposure

Scenario	Water(DtD)						Dermal		Inhalation	
	Drinking Water		Fish Ingestion							
	ADR mg/kg/day	LADD mg/kg/day	ADR mg/kg/day	LADD mg/kg/day	7Q10cc 170 ug/l	PDM Exceeded # Days	ADR mg/kg/day	LADD mg/kg/day	ADR mg/kg/day	LADD mg/kg/day
CEM User Defined Freq 3	--	--	--	--	--	--	1.38e-3	8.31e-6	7.65e-3	4.59e-5
CEM User Defined Freq 24	--	--	--	--	--	--	1.38e-3	6.65e-5	7.65e-3	3.67e-4

[redacted]

3.2 RISK CALCULATIONS

Inhalation risks for lung waterproofing were not quantified. As discussed under Section 2.4.1, the composition of [redacted] likely contained fluoralkene, fluorophenyl, and/or fluoroalcohol compounds. Fluoroalkenes and fluorophenyl compounds are unsaturated structures that are more reactive than fluoroalkanes, which make them susceptible to attack by nucleophiles. In contrast, the LVE substance contains a fluoralkane moiety, which will not undergo abiotic or biotic transformation to unsaturated alkenes or aromatic structures. Though the LVE substance may form a [redacted] due to acid hydrolysis in the stomach, this is a route specific pathway. The formation of a [redacted] would not be expected following inhalation exposures, due to the near neutral pH of pulmonary fluids.

Further, [redacted])[6] assessed pulmonary function in young adult volunteers, who performed [redacted] on two pairs of [redacted] in an unventilated room. The [redacted] time lasted for [redacted] and consisted of applying a [redacted], and then applying a [redacted] followed by brushing. The authors assessed pulmonary function using spirometry and single-breath carbon monoxide lung diffusion capacity (DI_{CO}) before and after the [redacted] and again [redacted]. No changes were reported in spirometry and DI_{CO} measurements. The authors concluded that moderate exposure to [redacted] had no significant effect on lung function

Therefore, EPA concludes that the potential risks to workers, general population, and consumers are negligible for lung waterproofing from inhalation exposures to the LVE substance.

[redacted] is not expected to form in the lungs. As noted under Section 1.1.1 for oral exposures, the LVE substance is expected to undergo acid hydrolysis in the stomach and enzymatic oxidation to [redacted]. In contrast, acid hydrolysis and enzymatic oxidation of the LVE substance will not occur in the pulmonary lumen of the conducting tubes. Though intracellular hydrolysis may occur *via* pulmonary carboxylesterases, this pathway is expected to be negligible given the estimated pulmonary absorption of the LVE substance (*i.e.*, nil or 0.1%).

Dermal risks were not quantified since there is not expected to be absorption of the parent compound by the skin.

Risks were quantified for drinking water exposures using [redacted]

3.2.1 Worker Calculations

Risks to workers for lung waterproofing via inhalation exposure were not assessed quantitatively because a structure–activity comparison between the analogue and the LVE substance indicate the LVE substance is unlikely to convey the same waterproofing characteristics as the analogue.

[6] [redacted]

[redacted]

Dermal risks were not evaluated since there is not expected to be exposure to the new chemical entrained in solid product as heated [redacted] due to the high temperature. Furthermore, absorption of the parent compound is estimated to be nil via dermal route.

3.2.2 General Population Calculations

Risks to the general population for lung waterproofing were not assessed quantitatively because a structure –activity comparison between the analogue and the LVE substance indicate the LVE substance is unlikely to convey the same waterproofing characteristics as the analogue. Furthermore, this acute, portal of entry effect is considered unlikely due to dilution of the new chemical substance in air immediately upon release, such that risks from inhalation exposure are expected to be negligible. There is no incineration, so there are no stack air release exposures. Risks were quantified for drinking water and fish ingestion scenarios using [redacted] data since this degradate is the chemical species in the general population exposures.

Population/Consumer Margin of Exposure (MOE) Calculations using Animal Oral POD and Exposure Report ADR

	Animal or Human			Human						Benchmark MOE	Endpoint Type
Exposure Route	POD mg/kg-day	POD Exposure Duration Days/Wk	POD Route % Absorp	Exposure mg/kg-day Acute Dose Rate (ADR)	Exposure Duration Days/Wk	Exposure Route % Absorp	Multiplier for Susceptible Subpopulations	Structural Alert as % of PMN	Margin of Exposure MOE	23000	LOAEL
Drinking Water (adult)	90.4	7	100%	5 66E-05	7	100%	1.0	100%	1,597,173	[redacted]	
Drinking Water (infant)	90.4	7	100%	5 66E-05	7	100%	4.17	100%	383,015		
Fish Ingestion	90.4	7	100%	8.47E-05	7	100%	1.0	100%	1,067,296		

Risks were not identified for the general population for systemic effects *via* drinking water or fish ingestion to a degradant [redacted] of the new chemical substance (MOEs $\geq$ 383,015; benchmark MOE = 23,000).

3.2.3 Consumer Calculations

Risks to consumers for lung waterproofing were not assessed quantitatively because a structure –activity comparison between the analogue and the LVE substance indicate the LVE substance is unlikely to convey the same waterproofing characteristics as the analogue. In support of this assumption, [redacted][7] provides evidence in humans that moderate exposure to [redacted] had no significant effect on lung function.

Dermal risks were not evaluated since there is not expected to be exposure to the new chemical entrained in solid product as heated [redacted] due to the high temperature. Furthermore, absorption of the parent compound is estimated to be nil via dermal route.

[7] [redacted]